JuanB Perez/DC/USEPA/US
09/16/2005 12:32 PM

To NCIC HPV@EPA
cc
bcc
Subject Fw: Robust Summary Submission for HPV Challenge Program

201-16033

----- Forwarded by JuanB Perez/DC/USEPA/US on 09/16/2005 12:31 PM -----

chip.witcher@syngenta.com

09/16/2005 08:55 AM

To NCIC OPPT@EPA, Rtk Chem@EPA
cc bill.secrest@syngenta.com, john.licata@syngenta.com, chris.howard@syngenta.com, jonathan.akins@syngenta.com, david.mizner@syngenta.com, brian.marable@syngenta.com, kim.rogers@syngenta.com, tim.pastoor@syngenta.com
Subject Robust Summary Submission for HPV Challenge Program

Dear Sir/Madam:

The attached information includes 1) a Robust Summary being submitted for the HPV Challenge Program, AR-201 in IUCLID format; and 2) a test plan identifying needed SIDS data and a strategy for fulfilling the test data requirements. The chemical substance covered by these submissions is isophthalonitrile (CAS 626-17-5). It was originally sponsored by Zeneca Ag Products, Inc. Syngenta Crop Protection, Inc. is the successor company to Zeneca Ag Products. We have searched our records and contacted EPA for assistance, but we have been unable to determine the original 7-digit HPV Challenge registry number assigned to this substance.

We will forward the results of environmental fate modeling covered in the test plan as soon as it is available.

<<ipn v1.rtf>> <<ipn test plan.doc>>
Syngenta Crop Protection, Inc. is also sponsoring two other HPV Challenge Program chemicals (4,4' - bipyridyl [CAS 553-26-4]; and benzonitrile, 3-methyl

[CAS 620-22-4]) that were originally sponsored by Zeneca Ag Products, Inc. The research for these submissions have been delayed beyond our intended July 2005 timeframe because it involves access to historical data files located in Europe. We anticipate that these submissions will be ready before the end of 2005.

Please send a confirmation that this information has been received and let us know if additional information is needed.

Thank you,

Chip Witcher

M.R. (Chip) Witcher, CIH
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TSCA Coordinator
Syngenta Crop Protection, Inc.
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ipn v1.rtf


ipn test plan.doc

Isophthalonitrile

CAS # 626-17-5

HPV Test Plan

Syngenta Crop Protection, Inc.

** July 2005

Summary

Syngenta Crop Protection, Inc (Syngenta) has agreed to participate in the United States Environmental Protection Agency's (EPA) voluntary High Production Volume (HPV) Chemical Program. The objective of EPA's HPV program is to provide basic hazard information for chemicals manufactured at high volumes in the United States. Syngenta hereby submits the test plan for isophthalonitrile (CAS# 626-17-5), which is used as an intermediate in the production of certain agricultural chemicals (e.g., fungicides).

IUPAC Name: Isophthalonitrile

Common Name: 1,3-dicarbonitrile benzene

Abbreviation: IPN

CAS#: 626-17-5

This document provides the test plan for isophthalonitrile (CAS# 626-17-5) under the High Production Volume (HPV) Chemical Challenge Program. The test plan identifies existing data of adequate quality for isophthalonitrile, and outlines any the intended testing to be conducted.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, Syngenta has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data according to guidance provided by the HPV program. The reliability of the studies were assessed based on the standards/guidances specified by the USEPA (Klimisch et al, 1997; US EPA, 1999).

Based on the amount, type and quality of hazard assessment data available for isophthalonitrile, no additional studies are currently needed to fulfill the SIDS data set.

Data Review
In developing a rationale for isophthalonitrile's test plan, Syngenta utilized data from internal studies and data from available publications. If the quality of the reports and data were of sufficient quality based on Klimische, 1997, then a robust summary was prepared describing the report and the data quality.

Physical/Chemical Properties
Robust summaries were developed for melting point, boiling point, vapor pressure and water solubility. Secondary literature sources were used to derive values for boiling point and water solubility. Data is available for all endpoints. (See Table 1 and IUCLID document).

Conclusion
In summary, the current physical/chemical property database for isophthalonitrile meets the HPV data requirements. No additional testing is required nor needed.

Environmental Fate
No specific environmental fate studies exist for IPN. However, environmental fate modeling should provide sufficient understanding of its potential movement in soil, water and air.

Conclusion
Syngenta needs to conduct environmental fate modeling using the known physical/chemical properties of IPN. Syngenta will update this document when modeling results become available.

Ecotoxicology
The acute toxicity (96 hr LC_{50} values) in traditional toxicity testing species of fish was reported to be 110 mg/l (Oncorhynchus mykiss) and 170 mg/l (Lepomis macrochirus). (See Table 1 and IUCLID document). One journal article mentioned the LC50 of 20 – 40 for a another species of fish (Oryzias latipes). The EC50 of 44 mg/L for algae, although the quality of this information was not sufficient for inclusion.

Conclusion
Based on the acute toxicity characteristics of isophthalonitrile, it should be categorized as practically nontoxic to trout and bluegill; IPN is slightly toxic to Oryzias latipes. While there are no data for aquatic invertebrates, it is unlikely isophthalonitrile would be categorized as highly toxic to aquatic invertebrates. There are no data on the toxicity of isophthalonitrile to aquatic or terrestrial plants, however isophthalonitrile is not known to have significant weed control efficacy. It is unlikely isophthalonitrile will pose a risk to aquatic invertebrates or plants.

Mammalian Toxicology

Significant and adequate toxicity testing of isophthalonitrile for purposes of hazard assessment currently exists. Mouse and rat acute oral toxicity studies and repeat dose toxicity studies meet the quality criteria. In addition, there is a one-generation reproduction study in the rat that also meets the quality criteria. (See Table 1 and IUCLID document).

Acute Toxicity

The acute toxicity of isophthalonitrile has been adequately evaluated in rats and mice. The acute oral LD_{50} value in rats was found to be 1790 mg/kg in males and 860 mg/kg in females. The acute oral LD_{50} value in mice was determined to be 369 mg/kg. (See Table 1 and IUCLID document).

Repeat Dose Toxicity

A 90-day dietary rat toxicity study was conducted with isophthalonitrile. The NOAEL was determined to be 1 mg/kg/day based on the increased incidence of hyaline droplet formation and abnormal accumulation of alpha-2 μ-globulin in kidneys at 5 and 25 mg/kg/day. However, it has been previously established that this effect is not relevant to humans, and, therefore, the NOAEL for females was 5 mg/kg/ day. The NOAEL in a 90-day dietary mouse study was 20 mg/kg/day. The NOAEL in a 21-day dermal study in rabbits was 500 mg/kg/day. In a 14-day inhalation study, increased liver weight was seen in both sexes at 190 and 1250 mg/m^3 but was not associated with any histopathological changes. (See Table 1 and IUCLID document).

Genetic Toxicity

IPN was reported to be negative in an Ames bacterial mutagenicity assay and Chinese hamster lung chromosomal aberration test. (See Table 1 and IUCLID document).

Reproductive and Development Toxicity

No developmental toxicity test has been conducted with isophthalonitrile, however a combination 28-day toxicity and one-generation reproduction study was conducted in the rat. (See Table 1 and IUCLID document). Rats were dosed at 0, 5, 10, 25 and 50 mg/kg/day up to 122 days. NOEL levels were determined to be 5 and 25 mg/kg/day for the 28-day toxicity and reproduction endpoints, respectively. No evidence of obvious/gross teratogenicity was noted in the one generation reproduction study.

Conclusion

For the purposes of satisfying HPV toxicity testing requirements for hazard assessment, it is concluded that no additional mammalian toxicity testing is necessary or required.

References

Klimisch HJ, Andreae M and Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25:1-5.

US EPA, 1999. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

Table 1. Available data for Isophthalonitrile (CAS# 626-17-5)

Endpoint	IPN
Physical-Chemical Data	
Molecular weight	106.15
Physical state	solid
Melting Point	162 ºC
Boiling Point	275 ºC
Vapor Pressure	1.77 hPa at 100°C
Partition Coefficient (logPow)	0.39
Water Solubility	soluble
Environmental Fate	
Photodegradation	No data
Fugacity (distribution)	No data
Biodegradability	No data
Water Stability	No data
Ecotoxicology	
Acute Fish Toxicity 96 hrs LC50	110 mg/l 170 mg/l
Acute Invertebrate Toxicity 48 hrs LC50	No data
Algal Toxicity LC50	44 mg/L (unacceptable quality)
Mammalian Toxicology	
Acute Toxicity Oral Inhalation Dermal	 LD50 = 1790 mg/kg bw (male rats), 860 mg/kg bw (female rats) 369 mg/kg bw mouse LC50 > 8970 mg/m^3 (1 hr, rats) LD50 > 2000 mg/kg bw (dermal, rabbits)
Mutagenicity	 Ames - negative Chromosome Aberration - negative
Repeated Dose Toxicity Feeding	 NOAEL 1 mg/kg/day rat NOAEL 20 mg/kg/day mouse

Inhalation Dermal (21 day)	NOAEL 190 mg/m^3 NOAEL 500 mg/kg/day rabbit
Reproductive Toxicity	~25 mg/kg/day
Developmental Toxicity	No data

*Robust summaries and References can be found in the IUCLID document.

Table 2. Test Plan for Isophthalonitrile

Endpoint	Data availability	Acceptable	Planned Testing
Physical-Chemical Data			
Molecular weight	✓	✓	No
Physical state	✓	✓	No
Melting Point	✓	✓	No
Boiling Point	✓	✓	No
Vapor Pressure	✓	✓	No
Partition Coefficient (logPow)	✓	✓	No
Water Solubility	✓	✓	No
Environmental Fate			
Photodegradation			
Fugacity (distribution)			
Biodegradability			
Water Stability			
Ecotoxicology			
Acute Fish Toxicity 96 hrs LC50	✓	✓	No
Acute Invertebrate Toxicity 48 hrs LC50	No	-	No
Algal Toxicity LC50	No	-	No
Mammalian Toxicology			
Acute Toxicity Oral Inhalation Dermal	 ✓ ✓ ✓	 ✓ ✓ ✓	No
Mutagenicity	✓	✓	No
Chromosome Aberration	✓	✓	No
Repeated Dose Toxicity	✓	✓	No
Reproductive Toxicity	✓	✓	No
Developmental Toxicity	No	-	No, based on

✓ Data available and considered adequate.

201-16033B

IUCLID

Data Set

Existing Chemical	:	ID: 626-17-5
CAS No.	:	626-17-5
EINECS Name	:	Benzene-1,3-dicarbonitrile
EC No.	:	210-933-7
Molecular Formula	:	C8H4N2

Producer related part

Company	:	Syngenta Crop Protection, Inc.
Creation date	:	09.09.2005

Substance related part

Company	:	Syngenta Crop Protection, Inc.
Creation date	:	09.09.2005
Status	:	
Memo	:	IPN 1ST DRAFT
Printing date	:	09.09.2005
Revision date	:	
Date of last update	:	09.09.2005
Number of pages	:	34
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	Cooperating company
Name	:	Syngenta Crop Protection, Inc.
Contact person	:	
Date	:	
Street	:	P.O. Box 18300
Town	:	NC 27419-8300 Greensboro
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	www.syngenta-us.com

30.06.2005

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Isophthalonitrile
Smiles Code	:	-
Molecular formula	:	C8H4N2
Molecular weight	:	128.14
Petrol class	:	-

29.06.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	Typical for marketed substance
Substance type	:	Organic
Physical status	:	Solid
Purity	:	> 99 % w/w
Colour	:	Light grey crystalline powder
Odour	:	Almond-like odour

29.06.2005

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,3-benzenedicarbonitrile

29.06.2005

1,3-dicyanobenzene

29.06.2005

IPN

29.06.2005

m-dicyanobenzene

29.06.2005

m-phthalodinitrile

29.06.2005

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : Industrial
Category : Chemical industry: used for chemical synthesis

29.06.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value : 5 mg/m3

29.06.2005

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information : No. 210-933-7

29.06.2005

Type : ENCS
Additional information : No. 3-1799

29.06.2005

Type : ECL
Additional information : No. KE-02185

29.06.2005

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 20.06.2005

29.06.2005

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 162 °C
Sublimation	:	-
Method	:	-
Year	:	-
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions 2G: Data from handbook or collection of data

07.07.2005 (10)

2.2 BOILING POINT

Value	:	= 275 °C at 1.033 hPa
Decomposition	:	-
Method	:	-
Year	:	-
GLP	:	No
Test substance	:	no data
Reliability	:	(2) valid with restrictions 2G: Data from handbook or collection of data

29.06.2005 (16)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 1.77 hPa at 100 °C
Decomposition	:	-
Method	:	-
Year	:	-
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions 2G: Data from handbook or collection of data

29.06.2005 (16)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	Octanol-water
Log pow	:	= 0.39 at 25 °C
pH value	:	-
Method	:	OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year	:	1982

GLP	:	no data
Test substance	:	-
Remark	:	The low partition coefficients log Pow of 0.39 for m-PDN suggests that there will be not be accumulation in organisms.
Test substance	:	Analytical grade IPN
Reliability	:	(2) valid with restrictions 2B Guideline study with acceptable restrictions

07.07.2005 (18)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 0.08 vol% at 20 °C
pH value	:	-
concentration	:	at °C
Temperature effects	:	-
Examine different pol.	:	-
pKa	:	-
Description	:	-
Stable	:	-
Deg. product	:	-
Method	:	-
Year	:	-
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions 2G: Data from handbook or collection of data

29.06.2005 (16)

Remark	:	Slightly soluble in hot water, very soluble in hot alcohol, ether and benzene, insoluble in petroleum ether.
Reliability	:	(2) valid with restrictions 2G: Data from handbook or collection of data

07.07.2005 (10)

2.6.2 SURFACE TENSION

Remark : No data
29.06.2005

2.7 FLASH POINT

Remark : No data
29.06.2005

2.8 AUTO FLAMMABILITY

Remark : No data
29.06.2005

2.9 FLAMMABILITY

Remark : No data
29.06.2005

2.10 EXPLOSIVE PROPERTIES

Remark : No data
29.06.2005

2.11 OXIDIZING PROPERTIES

Remark : No data
29.06.2005

2.12 DISSOCIATION CONSTANT

Remark : No data
29.06.2005

2.13 VISCOSITY

Remark : No data
29.06.2005

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Semistatic
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 170 measured/nominal
Limit test	:	-
Analytical monitoring	:	yes
Method	:	other: OECD 403 and EPA 40 CFR 797: 1400
Year	:	1991
GLP	:	Yes
Test substance	:	Isophthalonitrile

Result : The pH value of the test solutions during the test varied between 7.5 and 7.6. The oxygen saturation in all test vessels was between 8.2 and 8.8 mg O2/l. The temperature was between 20.5 and 22.0 oC. The mean measured concentrations were 26, 40, 60, 90, 130 and 210 mg/l. The difference between nominal concentrations and mean measured concentrations were considered to be within acceptable limits. The LC50 was determined to be 170 mg/l (95% confidence limits 150-190 mg/l).

Test condition : The test organism:
Bluegill sunfish (Lepomis macrochirus) were obtained from Monkfield Aquatics, Cambridge, UK. Fish with a mean length of 3.2 cm ± 0.3 cm (range 2.7 - 3.9 cm) and mean weight of 0.68 g ± 0.29 g were used for testing. The standard length of the fish used in this study were slightly greater than that set down by the OECD guidelines (2 ± 1 cm) but this is not considered to have a significant effect on the results of the test. No feeding occurred 48 hrs before the test and during the test. Biological loading was 0.34 g/l test liquid. Light dark cycle was 16/8 hours.

Test Solutions
The nominal test concentrations were 30, 45, 68, 100, 150 and 220 mg/l. Reconstituted water was tested as control. 20 fish were used for each test concentration and for the control. Exposure period was semi-static for 96 hrs. pH, dissolved oxygen and temperature were measured in the test solutions and in the control at the start and at 24, 48, 72 and 96 hours. No auxiliary aeration was employed during the study.

Test Design
20 litre glass jars were used as test vessels. The temperature during the test was 12 ± 1 oC. Mortality and abnormal behaviour were recorded every 24 hrs. Each day the fish were transferred to freshly prepared test liquids in new test vessels. Sampling from the test vessels was performed at the test start and after 24 hours and 96 hours. Analysis of samples was performed by capillary GC.

Statistical Analysis
LC50 values were determined using Probit-analysis.

Test substance : Isophthalonitrile 98.8% a.i. pure, supplied by ISK Biotech Corp.

Reliability : (1) valid without restriction
1A: GLP guideline study

20.07.2005 (7)

Type	:	Semistatic
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 110 mg/l

Limit test	:	-
Analytical monitoring	:	Yes
Method	:	other: OECD 403 and EPA 40 CFR 797: 1400
Year	:	1992
GLP	:	Yes
Test substance	:	Isophthalonitrile

Result : The pH value of the test solutions during the test varied between 7.7 and 7.9. The oxygen saturation in all test vessels was between 9.9 and 10.7 mg O2/l. The temperature was 11-12 oC. The mean measured concentrations were 15, 22, 33, 49, 72, and 110 mg/l. The difference between nominal concentrations and mean measured concentrations were considered to be within acceptable limits. The LC50 was determined to be 110 mg/l (95% confidence limits 93-117 mg/l. 110 mg/l was the highest test concentration that could be prepared during overnight stirring, and this level represents a saturated solution for the given test temperature and test water.

Test condition :

Test Organism
Rainbow trout (Oncorhynchus mykiss) were obtained from laboratory stock culture, the original population having been obtained from Westacre Trout Farm, Norflok. Trout with a mean length of 4.6 cm ± 0.4 cm and mean weight of 1.32 g ± 0.37 g were used for testing. No feeding occurred 48 hrs before the test and during the test. Biological loading was 0.66 g/l test liquid. Light dark cycle was 16/8 hours.

Test Solutions
The nominal test concentrations were 20, 30, 45, 68, 100 and 150 mg/l. Reconstituted water was tested as control. 20 fish were used for each test concentration and for the control. Exposure period was semi-static for 96 hrs. pH, dissolved oxygen and temperature were measured in the test solutions and in the control at the start and at 24, 48, 72 and 96 hours. No auxiliary aeration was employed during the study.

Test Design
20 litre glass jars were used as test vessels. The temperature during the test was 12 ± 1 oC. Mortality and abnormal behaviour were recorded every 24 hrs. Each day the fish were transferred to freshly prepared test liquids in new test vessels. Sampling from the test vessels was performed at the test start and after 24 hours and 96 hours. Analysis of samples was performed by capillary GC.

Statistical Analysis
LC50 values were determined using Probit-analysis.

Test substance : Isophthalonitrile 98.0% a.i. pure, supplied by ISK Biotech Corp.

Reliability : (1) valid without restriction
1A: GLP guideline study

20.07.2005 (8)

Type	:	-
Species	:	Oryzias latipes (Fish, fresh water)
Exposure period	:	-
Unit	:	-
24 hr TLm (mg/l)	:	= 40 mg/l measured/nominal
48 hr TLm (mg/l)	:	= 22 mg/l measured/nominal
Limit test	:	No
Analytical monitoring	:	
Method	:	Other: Japanese industrial standards committee (1971) Testing methods for industrial wastewater. JIS K0102 p154.
Year	:	1982
GLP	:	no data
Test substance	:	Isophthalonitrile

Test substance	:	Analytical grade IPN
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

06.07.2005 (18)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Algae
Endpoint	:	Other: Growth Inhibition
Exposure period	:	72 hour(s)
Unit	:	mg/l
EC50	:	= 44 mg/l
Reliability	:	(4) not assignable 4C: Original reference not yet available

20.07.2005 (17)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male/female
Number of animals	:	45
Vehicle	:	CMC
Doses	:	Male rats were dosed at levels of 900, 1250, 1800 and 2500 mg/kg. Female rats were dosed at levels of 650, 750, 900, 1250 and 1800 mg/kg
Method	:	Other (calculated)
Year	:	1986
GLP	:	Yes
Test substance	:	Isophthalonitrile

Method :

Number of animals: 5 males and 5 females per dose level; 45 rats total.

Age: Young adult

Dose/ Concentration: Administered orally by gavage. Male rats were dosed at levels of 900, 1250, 1800 and 2500 mg/kg. Female rats were dosed at levels of 650, 750, 900, 1250 and 1800 mg/kg. Dose volume was 10ml/kg.

Vehicle: Isophthalonitrile was administered orally as a suspension in 0.5% (w/v) aqueous carboxymethyl cellulose.

Post dose observation period: 14 days

Study design: All rats were necropsied for gross pathological lesions.

Result :

LD50: The median lethal dose (LD50) for isophthalonitrile, administered orally to Charles River CD (Sprague Dawley) rats was 1790 mg/kg with 95% confidence limits of 1170 to 2760 mg/kg for males and 860 mg/kg with 95% confidence limits of 670 to 1090 mg/kg for females.

Number of deaths: Mortality rates are reported for each for each dose level. Mortality occurred from day 1 through day 4, with most deaths occurring on days 1 and 2.

Mortality

Dose(mg/kg)	Males	Females
605	-	0/5
750	-	2/5
900	1/5	4/5
1250	1/5	4/5
1800	2/5	5/5
2500	4/5	-

Clinical observations noted that were considered to be directly related to compound administration were lethargy, ataxia, increased secretions (salivation and bilateral clear ocular discharge respiratory distress), eye closure, convulsions, hypothermia, prostration, tremors and urogenital

staining. Dried red material around the eyes, mouth and/or nose were present in more than one-half of all rats on study. This is a typical finding in rats that have been stressed and was considered an indirect effect of test material administration. In general, these clinical findings were observed early in the study with generally no apparent pattern or relationship to dosage. Gross pathology changes considered to be treatment related included gastric effects, intestinal effects, pulmonary effects, brain effects and renal effects.

Test substance : Isophthalonitrile 99.3% pure, provided by SDS Biotech Corporation, Houston, TX.

Conclusion : Based on the differing mortality pattern between males and females, an LD50 based on combined mortality data for male and female rats was not calculated.

Reliability : (1) valid without restriction
1B: Comparable to guideline study

20.07.2005 (6)

Type : LD50
Value : > 5010 mg/kg bw
Species : Rat
Strain : -
Sex : Male/Female
Number of animals : 10
Vehicle : CMC
Doses : 5010 mg/kg
Method : Oral
Year : 1972
GLP : No
Test substance : no data

Method : IPN was administered orally, as a suspension in 0.5% carboxymethyl cellulose at a dose of 5010 mg/kg bodyweight to 5 male and 5 female rats. The animals were observed for 14 days after dosing.

Result : There were no deaths or adverse effects noted after the 14 day observation period.

Conclusion : The LD50 of IPN is greater than 5000 mg/kg bw in the rat.

Reliability : (3) invalid
3A: Documentation insufficient for assessment.

20.07.2005 (13)

Type : LD50
Value : mg/kg bw
Species : Mouse
Strain : CD-1
Sex : Male/female
Number of animals : 50
Vehicle : CMC
Doses : 180, 280, 360, 450 and 560 mg/kg.
Method : Other (calculated): EPA TSCA FR 50, No. 188, PART 798 (1985)
Year : 1992
GLP : Yes
Test substance : Isophthalonitrile

Method : Age: Young Adult

Dose/ Concentration: Administered orally by gavage at dose levels of 180, 280, 360, 450 and 560 mg/kg. Dose volume was 20 ml/kg.

Vehicle: Isophthalonitrile was administered orally as a suspension in 0.5% (w/v) aqueous carboxymethyl cellulose.

Post dose observation period: 14 days

Result : Study design: All mice were necropsied for gross pathological lesions.
Number of deaths: Mortality rates are reported for each dose level.

Mortality

Dose level (mg/kg)	Males	Females
180	0/5	0/5
280	1/5	4/5*
360	2/5	1/5
450	2/5	4/5
560	5/5	5/5

*The cause of death of two of the four females at 280 mg/kg was gavage error; therefore, these animals were not included in the calculation of the LD50

Compound-related clinical observations noted at 280 mg/kg and higher included decreased activity, labored breathing, prostration, tremors, convulsions, and hunched posture. Prior to death, decreased feces and hypothermia were seen. No abnormal clinical signs were observed in surviving mice after Day 4 of the study. All mice administered 180 mg/kg appeared normal throughout the observation period. Necropsy findings included anogenital staining in 12 out of 24 mice found dead during the study. In addition, clear, colorless liquid was noted around the eyes, nose and/or mouth was noted in one female at 450 mg/kg and one male at 560 mg/kg. The only internal findings noted were torn esophagus and brown material in the thoracic cavity in two females from the 280 mg/kg group confirming that these two animals died due to gavage errors.

Test substance : Isophthalonitrile 99.9% pure, supplied by ISK Biotech Corp.
Conclusion : LD50: The median lethal dose (LD50) of isophthalonitrile when administered to male and female CD-1 mice was 369 mg/kg with 95% confidence limits of 321 to 424 mg/kg. The No-Observed-Effect Level (NOEL) was 180 mg/kg.
Reliability : (1) valid without restriction
1A: GLP guideline study
Flag : Critical study for SIDS endpoint
20.07.2005 (20)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : > 8970 mg/m³
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 30
Vehicle : -
Doses : 490, 2410 and 8970 mg/m³
Exposure time : 1 hour(s)
Method : Inhalation
Year : 1972
GLP : No
Test substance : Isophthalonitrile

Method : Study design: Three (3) groups (5 males and 5 females per grp) were exposed for one (1) hour to one of three aerosol concentrations. The solid particulate aerosol was generated by using a fluidized bed technique. Bodyweights were measured on days -1 7 and 14. The animals were sacrificed and necropsied after the 14 day observation period.

Result	:	There were no significant clinical signs exhibited during the 1 hr exposure period. Post exposure all animals in all groups showed signs of rhinorrhea. This observation had cleared by the 2nd day post-exposure. Average bodyweights of the female rats in groups 1 and 3 were reduced during the second week of the observation period. All other animals gained weight normally. No deaths occurred during the study. Gross pathological changes were seen in the lungs of rats in groups 1 and 3 (hemorrhagic). The lungs from rats in group 2 were normal.
Test substance	:	Isophthalodinitril, sieved through an 18-mesh (1/18 in) sieve before use. Not further data available
Conclusion	:	Rats exposed to IPN up to 8970 mg/m³ showed no treatment related effects. The LC50 of IPN is greater than 8970 mg/m³ in rats.
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (12)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	Rabbit
Strain	:	-
Sex	:	Female
Number of animals	:	10
Vehicle	:	-
Doses	:	2000 mg/kg bw
Method	:	Dermal
Year	:	1972
GLP	:	No
Test substance	:	Isophthalonitrile
Method	:	Test material was applied to the clipped skin of 5 female rabbits and to the clipped and abraded skin of 5 female rabbits. This remained in contact with the skin for 24 hours. The trunk of each rabbit was covered with a dam to prevent loss of the test material. After 24 hours the test material and any residue was washed off with water. Animals were observed for 14 days after dosing. Individual bodyweights were recorded on days 0, 3, 7, 10 and 14.
Result	:	One animal died on day 7 due to a prolapsed uterus. No further deaths were reported. No erythema or oedema were reported for any of the animals exposed to IPN.
Test substance	:	IPN, White powder. No further details available
Conclusion	:	The acute dermal LD50 is greater than 2000 mg/kg bw in the rabbit.
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

04.07.2005 (11)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	Rabbit

Concentration	:	500 mg
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	12
Vehicle	:	-
PDII	:	0
Result	:	Not irritating
Classification	:	Not irritating
Method	:	Draize Test
Year	:	1972
GLP	:	No
Test substance	:	Isophthalonitrile

Method : 2 groups of 6 female New Zealand albino rabbits had 500 mg of test material applied to intact or abraded skin. The test material was covered and left for 24 hours. After 24 hours the binders and the tape were removed and the skin assessed using the Draize technique. A subsequent evaluation of the skin was also made at 72 hours after application.

Result : Erythema and Edema scores were 0 (zero) for all for intact and abraded rabbit skin.

Test substance	:	IPN, No further details given
Conclusion	:	IPN was not irritant to intact or abraded skin in the rabbit.
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (15)

5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	-
Dose	:	50 other: mg
Exposure time	:	-
Comment	:	-
Number of animals	:	7
Vehicle	:	None
Result	:	not irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1972
GLP	:	No
Test substance	:	Isophthalonitrile

Method : New Zealand White rabbits had a single 50 mg application of IPN into the conjunctival sac of the left eye. The lids were held together for one second and the animal released. Four animals (group 1) had their eyes washed with 300ml tap water for 2 minute period 5 minutes after exposure and were examined at 1 hour. The remaining 3 animals (group 2) were examined at 1 hour but not washed until 24 hours. The right eye of each animal served as a control and remained untreated. Gross signs of eye irritation and systemic toxicity were recorded at 1, 24, 48 and 72 hours and 7 days following application. Eye irritation was scored according to the grades for ocular reaction as cited in the Federal Register, Vol 37, No. 83 Fri April 28, 1971, pg. 8534-8535.

Result : Group 1 – slight redness in one rabbit at 24 hrs, which returned to normal at 48 hours. All other eyes were scored at 0 (zero).

Group 2 - all rabbit eyes were negative - score 0 (zero).

Test substance	:	IPN, White powder - considered to be 100% purity
Conclusion	:	IPN was not an eye irritant to the rabbit.
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (14)

5.3 SENSITIZATION

Remark	:	No data

04.07.2005

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Inhalation
Exposure period	:	6 hrs/day
Frequency of treatm.	:	Five days per week for two consecutive weeks
Post exposure period	:	-
Doses	:	0, 200, 1500 mg/m3
Control group	:	yes, concurrent no treatment
NOAEL	:	= 190 mg/m³
Method	:	Inhalation
Year	:	1972
GLP	:	No
Test substance	:	Isophthalonitrile

Method : Doses/concentration level: 0, 200 mg/m3 nominal concentration (190 mg/m3 actual) and 1500 mg/m3 nominal concentration (1250 mg/m3 actual). The solid particulate aerosol was generated using a fluidized bed technique.

Exposure period: Six hours per day

Frequency of treatment: Five days per week for two consecutive weeks

Number of animals: 30 total, five male and five female per group.

Control group and treatment: Clean air only for five days per week for two consecutive weeks.

Statistical methods: All statistical evaluations were performed using the nonparametric Mann-Whitney U test.

Study design:
All animals were observed for pharmacotoxic signs daily. Body weight and food consumption data were collected weekly. The hematological parameters of hematocrit, erythrocyte count, hemoglobin concentration, total and differential leucocyte count were evaluated prior to exposure and at necropsy after the last exposure. A complete necropsy was performed and histopathology was performed on the trachea, lungs, liver and kidneys.

Result : Toxic response/effects by dose level: The two groups of exposed animals exhibited some loss of body weight, decreased food consumption and

alopecia. The high level group (1250mg/m3) also exhibited rhinorrhea and diarrhea. All these effects were classified as moderate in degree and were not seen in the control group. The hematologic data revealed a number of statistically significant differences between the exposed and control groups. However, all the values are well within the normal range and the direction of the differences are not consistent. There were some statistically significant differences in absolute organ weights and organ weights as a percentage of body weight, particularly liver weights. However, these effects were not evident with microscopic examination of the tissues. There were no gross pathological abnormalities observed at necropsy and there were no exposure-related histological alterations noted in any of the tissues examined from the exposed animals.

Test substance : Isophthalonitrile. No further details given
Conclusion : The NOAEL of IPN in this study is 190 mg/m3
Reliability : (2) valid with restrictions
2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (3)

Type : Sub-chronic
Species : Rat
Sex : Male/female
Strain : other: Charles River Crl:CD BR VAF/PLUS©
Route of admin. : Oral feed
Exposure period : 99 days
Frequency of treatm. : daily in diet
Post exposure period : -
Doses : 0, 1, 5 and 25 mg/kg/day
Control group : Yes
NOAEL : = 1 mg/kg bw
Method : -
Year : 1992
GLP : Yes
Test substance : Isophthalonitrile

Method : Control group and treatment: Control animals were fed Purina© Certified Rodent Chow No. 5002 without test substance ad libitum and fresh tap water was available ad libitum.

Study design: Ten (10) rats per sex were used to establish baseline clinical pathology parameters.

Result : NOAEL (NOEL): The NOEL for males was 1 mg/kg/day, based on the increased incidence of hyaline droplet formation with abnormal accumulation of alpha-2 m-globulin at 5 and 25 mg/kg/day. The NOEL in females was 5 mg/kg/day, based on increases in GGT, urine volume, relative liver weight and centrilobular hepatocytomegaly at 25 mg/kg/day.

Toxic response/effects by dose level: Isophthalonitrile was administered in the diet at dose levels of 0, 1, 5 and 25 mg/kg/day for at least 99 days.

Mean Food Consumption

Sex	Nominal Dose Level (mg/kg/day)	Mean Compound Consumption (mg/kg/day)
M	1	1.0
F	1	1.0
M	5	4.9
F	5	5.0
M	25	24.9

F 25 25.3

Compound-related effects on body weight and body weight gain with associated changes in food consumption were observed in males at 25 mg/kg/day during the study. A compound-related increase in urine volume was noted in females at 25 mg/kg/day, but no corroborating evidence, e.g., gross or microscopic finding in the kidney was found. Absolute and relative (to body and brain) kidney and adrenal weight were higher in males at 25 mg/kg/day than controls. In addition, liver weight relative to body and brain weight was higher in males and females at 25 mg/kg/day than respective control animals. Histopathologic examination revealed compound-related increases in the incidence of centrilobular hepatocytomegaly in males at 25 mg/kg/day. Although the increase was not considered significant by the pathologist, 2 of 15 females also exhibited centrilobular hepatocytomegaly. Considering the increased incidence in males, the increase in relative liver weight in females, a significant increase in GGT in the high dose females and the results of a previously conducted 28-day study, the appearance of this lesion in females was considered by the Study Director to be compound related. A compound related increase in hyaline droplet formation was noted in males at 5 and 25 mg/kg/day when compared to controls. No females exhibited this finding. Hyaline droplet formation in the proximal tubular epithelium of kidneys in male rats is indicative of abnormal accumulation of alpha-2 m-globulin, a protein reported to be unique to the rat. Based on this effect, therefore, the No-Observed-Effect Level (NOEL) was considered separately for males and females.

Test substance : ISOPHTHALONITRILE (CAS # 626-17-5) Test material provided by ISK Biotech Corporation. The test material was characterized for purity and identity prior to initiation and after completion of the study. Results indicated the test material was greater than 98% pure and was stable throughout the duration of the study.

Conclusion : The NOAEL for males was 1 mg/kg/day based on the increased incidence of hyaline droplet formation and abnormal accumulation of alpha-2 m-globulin in kidneys at 5 and 25 mg/kg/day. This effect is not relevant to humans.

Reliability : (1) valid without restriction
1B: Comparable to guideline study

20.07.2005 (5)

Type : Sub-acute
Species : Mouse
Sex : male/female
Strain : CD-1
Route of admin. : Oral feed
Exposure period : Up to 35 Days
Frequency of treatm. : Daily in the diet
Post exposure period : -
Doses : 0, 1500, 2250 and 3000 ppm
Control group : Yes
Method : -
Year : 1992
GLP : Yes
Test substance : Isophthalonitrile

Method : Doses of IPN at 0, 1500, 2250 and 3000 ppm in the diet.

Age at study initiation: Mice (Charles River Crl:CD-1 (ICR)BR VAF/PLUS©) were 27 days of age at receipt and 42 days of age at initiation of the test material administration.

Control group and treatment: Control animals were fed Purina© Certified Rodent Chow No. 5002 without test substance ad libitum and fresh tap

water was available ad libitum.

Study design: Clinical observations were performed daily during the study beginning at initiation of test material administration. During the observations, animal was handled and it general condition assessed. Individual body weights and food consumption were recorded weekly from one week prior to initiation of test material administration to study termination. The concentrations of isophthalonitrile in the diet were constant throughout the study. The achieved doses were calculated at the end of each week. Daily food consumption, food consumption relative to body weight, and compound consumption were calculated for individual animals. After at least 34 days on test diets, blood samples were collected from all surviving animals for clinical chemistry and hematology parameters. Food was withheld 16 to 20 hours prior to blood collection. All animals were subjected to a complete necropsy. Brain, liver, kidneys, adrenals and gonads were weighed. Lungs, liver, spleen, kidneys, testes, epididymides, ovaries, uterus and gross lesions were evaluated microscopically.

Result : NOAEL (NOEL): A No-Observed-Effect Level (NOEL) was not identified in this study because of the compound-related effects observed at all levels of treatment. Dietary levels for the subsequent 90-day study in mice were selected to be 0, 125, 1250 and 3000 ppm for males and 0, 25, 1250 and 2250 for females. The high dose level selected for females was lower than the level chosen for males because of the excessive mortality noted in females at 3000 ppm.

Toxic response/effects by dose level: The liver appeared to be the target organ. Compound-related, statistically significant increases in absolute and relative (to body and brain weight) liver weight and centrilobular hepatocytomegaly were noted in both males and females at all dietary levels. Other compound-related findings included a 50% mortality rate in females at 3000 ppm and clinical signs of toxicity at all dietary concentrations which included few or no feces, increased activity and aggressiveness. Severe losses in body weight and a reduction in food consumption during the first week on the test diets followed by compensatory increases in body weight gain in males and females from all test groups suggested a palatability problem and subsequent adaptation to the taste of the test material. Food consumption, unlike body weight gain, did not recover in the test groups after the first week but remained below that of the controls throughout the study.

Mean Food Consumption

Sex	Dietary Conc. (ppm)	Mean Dose Level (mg/kg/day)
M	1500	259
F	1500	305
M	2250	399
F	2250	466
M	3000	501
F	3000	617

No compound-related effects on hematology were observed in males during this study. An apparent decrease in lymphocyte count and increase in neutrophil count were noted in females fed 2250 ppm. This may be a secondary effect of reduced food consumption. The following statistically significant increases in clinical chemistry parameters were noted in high dose males when compared to controls: ALT, albumin, A/G ratio, total protein and sodium. GGT was increased in high dose males, and cholesterol was higher in mid and high dose males than controls, although not statistically significant. Significant increases in ALT, cholesterol, GGT, BUN, and globulin and significant decreases in potassium were noted in

females at 3000 ppm. A significant increase in cholesterol and decrease in potassium were noted in females at 2250 ppm. The significant increase in ALT, cholesterol and GGT in high dose males and females were suggestive of a liver effect which was corroborated by increased absolute and relative liver weight and microscopic evidence of liver damage. The other changes in clinical chemistry parameters were not accompanied by changes in organ weights or microscopic findings and therefore are not considered to be related to isophthalonitrile administration. No compound-related findings were noted at necropsy. Histopathology indicated an increased incidence of centrilobular hepatocytomegaly in the liver of the majority of treated males and females in the study. The high dose females that died during the study did not exhibit this lesion, suggesting they were not exposed to the test material for an adequate period of time to develop hepatocytomegaly. The severity of the lesion increased with increasing dosage and ranged from minimal to moderate.

Test substance : ISOPHTHALONITRILE (CAS # 626-17-5) Test material provided by ISK Biotech Corporation. The test material was characterized for purity and identity prior to initiation and after completion of the study. Results indicated the test material was greater than 99% pure and was stable throughout the duration of the study.

Conclusion : A No-Observed-Effect Level (NOEL) was not identified in this study because of the compound-related effects observed at all levels of treatment.

Reliability : (1) valid without restriction
1B: Comparable to guideline study.

06.07.2005 (19)

Type : Sub-chronic
Species : Mouse
Sex : Male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : At least 91 days
Frequency of treatm. : Daily
Post exposure period : -
Doses : 0, 125, 1250 and 3000 ppm for males and 0, 125, 1250 and 2250 ppm for females.
Control group : Yes
NOAEL : = 20 mg/kg bw
Method : -
Year : 1993
GLP : yes
Test substance : Isophthalonitrile

Method : Doses/concentration level: 0, 125, 1250 and 3000 ppm for males and 0, 125, 1250 and 2250 ppm for females.

Number of animals: 10 mice (Charles River Crl:CD-1(ICR) BR VAF/PLUS©) of each sex per dose group.

Age at study initiation: Mice were 28 days of age at receipt and 48 days of age at initiation of the test material administration.

Control group and treatment: Control animals were fed Purina© Certified Rodent Chow No. 5002 without test substance ad libitum and fresh tap water was available ad libitum.

Study design: An additional 10 mice of each sex were included in each group and were used to evaluate effects on clinical pathology after 30 days exposure to isophthalonitrile.

Result : NOAEL (NOEL): 125 ppm

Toxic response/effects by dose level: All animals, except one female, in the high dose group exhibited few or no feces during the first week of exposure. Two mid dose females also exhibited this sign. This observation coincided with the severe reduction in food consumption and body weight observed during the first week of exposure. By the end of Week 2, the sign was no longer present. Body weights were consistently lower than controls in males at 3000 ppm (high dose) throughout the study. In females, significantly lower body weight was noted during Week 1 at 1250 ppm (mid dose) and Weeks 1 and 2 at 2250 ppm (high dose). Although full recovery of body weight was noted in mid and high dose females and in mid dose males, the terminal body weight of high dose males was significantly lower than controls indicating that these animals did not fully recover the weight lost during Week 1. A statistically significant reduction in food consumption was noted in high dose males and females during Week 1 through Week 4 and Week 6 of the study. At 1250 ppm, significantly lower consumption was observed during Weeks 1, 3 and 4 in males and Weeks 1 and 3 in females. No compound-related effects in food consumption were noted in males and females fed 125 ppm.

Mean Food Consumption

Sex	Dietary Conc. (ppm)	Mean Dose Level (mg/kg/day)
M	125	20
F	125	23
M	1250	194
F	1250	227
M	3000	471
F	2250	369

Compound-related increases in cholesterol, total protein, albumin, and AST were noted in females at 2250 ppm and males at 3000 ppm. Absolute and relative (to body and brain) liver weights were higher in males and females at 1250 ppm and higher doses. Histopathologic examinations revealed compound-related increases in the incidence of centrilobular hepatocytomegaly in both sexes at 1250 ppm and higher. An increase in absolute and relative adrenal weight, possibly associated with microscopic evidence of cortical hypertrophy, was noted in males at 3000 ppm. In females, decreased relative ovary weight and microscopic evidence of reduced cyclic activity in the ovary were noted at 1250 ppm and higher.

Test substance : ISOPHTHALONITRILE (CAS # 626-17-5) Test material provided by ISK Biotech Corporation. The test material was characterized for purity and identity prior to initiation and after completion of the study. Results indicated the test material was greater than 99% pure and was stable throughout the duration of the study.

Conclusion : The NOAEL is 20 mg/kg/day

Reliability : (1) valid without restriction
1B: Comparable to guideline study.

06.07.2005 (4)

Type : Sub-acute
Species : Rabbit
Sex : Male/female
Strain : New Zealand white
Route of admin. : Dermal
Exposure period : 21 Days
Frequency of treatm. : -
Post exposure period : No data available
Doses :
Control group : Yes

NOAEL : = 500 mg/kg bw
Method : -
Year : 1972
GLP : no
Test substance : Isophthalonitrile

Method : Doses/concentration level: 0, 0.5, 1.0 and 2.0 g/kg

Exposure period: 6 hours per day for 5 days per week

Frequency of treatment: 5 days per week for 3 weeks. Test material was applied at 9 AM 5 days a week for 3 consecutive weeks. Six hours later the residue was gently washed off. During the 6 hour period, the animals were equipped with a collar to prevent ingestion of the test material.

Number of animals: 40 total. 10 per group; 5 male and 5 female. Of the 5 males and 5 females in each group, 2 were clipped with intact skin and 3 were clipped with abraded skin.

Control group and treatment: The control animals were treated in the same manner but received only distilled water in a volume equal to that of the highest treatment group.

Study Design:
Clinical signs - physical appearance and behavior were observed daily.
Body weight and food consumption - recorded weekly.

Observation of skin reactions - erythema and edema were scored
Hematology - blood samples taken prior to treatment and at sacrifice
Blood chemistry - blood samples taken prior to treatment and at sacrifice
Urinalysis - urine was collected over an 18 hour period from animals in fasting state for analysis

Gross pathology was observed, organ weights recorded, and selected sections of spleen, liver, kidney, urinary bladder and skin were examined microscopically.

Post exposure observation period: Not specified

Result : Toxic response/effects: The repeated dermal application of isophthalonitrile at 0.5, 1.0 and 2.0 g/kg of body weight to the abraded and unabraded skin of rabbits, five days a week for a period of three weeks, did not cause any dermal irritation. Also, no evidence of systemic toxicity was noted in the sections of spleen, liver, kidney, or urinary bladder from the treated animals.
There were no remarkable behavioral observations noted. One rabbit was found dead on Day 17 of the study (2.0 g/kg group) apparently due to a respiratory problem. Cause of death could not be established by histopathology. Body weight changes were comparable in control and treated groups, except in females treat with the highest dose. In this group, all animals lost some weight during the study. Food consumption was similar in control and treated groups. There were no changes in hematology that which could attributed to treatment. There was some indication of increased SGPT values in some of the treated animals, but those changes did appear to be related dose. There were no effects noted in the urinalysis values. The group mean values for spleen weights suggest spleens were smaller than controls in male and female at the 2.0 g/kg treatment level and that ovaries and thyroids were smaller in females in the 1.0 and 2.0 g/kg treatment groups. In the case of the spleen values, the individual animal values show that an occasional high or low value accounted for the differences. No related histopathological changes were noted in any of these organs.

Test substance	:	Isophthalonitrile was mixed with distilled water on a 50% weight to volume basis to form a thick paste. No further details available.
Conclusion	:	The NOAEL for this study is 500 mg/kg/day.
Reliability	:	(2) valid with restrictions 2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (2)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Bacterial test with and without activation
Test concentration	:	0, 313, 625, 1250, 2500 and 5000 µg/plate, -S9 mix and +S9 mix.
Cycotoxic concentr.	:	-
Metabolic activation	:	With and without
Result	:	Negative
Method	:	OECD Guide-line 471
Year	:	1996
GLP	:	yes
Test substance	:	Isophthalonitrile

Method : Bacterial test with and without activation

Species/strain: Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvrA

Metabolic activation: Rat liver, induced with phenobarbital and 5,6-benzoflavone

Positive controls: -S9 mix, 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, WP2, TA98), Sodium azide (TA1535) and 9-Aminoacridine (TA1537), +S9 mix, 2-Aminoanthracene (five strains)

Result : This chemical did not induce gene mutations in the S. typhimurium. Toxicity was not observed at 5000 µg/plate in the five strains either without S9 mix or with S9 mix.

Test substance	:	Isophthalonitrile. No further details given
Conclusion	:	Isophthalonitrile did not induce gene mutations in this bacterial test with and without activation
Reliability	:	(1) valid without restriction 1A: GLP guideline study

20.07.2005 (9)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster lung (CHL/IU) cells
Test concentration	:	-
Cycotoxic concentr.	:	-
Metabolic activation	:	-
Result	:	Negative
Method	:	OECD Guide-line 473
Year	:	1996
GLP	:	-
Test substance	:	Isophthalonitrile

Method : The chromosomal aberration test was conducted using Chinese hamster lung CHL/IU cells. The cells were cultured with Eagle's minimum essential medium (MEM) supplemented with 10% fetal calf serum or calf serum. The cells were plated in 5ml medium on 60mm plate and cultured for 72 h at

37C in a humidified incubator (5% CO2) before the treatment. To examine the metabolic activation of the chemicals, the proliferating cells were treated with the chemicals for 6 hrs in serum-free MEM with S9 mix (S9(+)), or without S9 mix (S9(-)), then cultured a further 18 hrs in the fresh MEM with serum. The cells were treated for 24 and 48 hrs continuously in the absence of S9 mix. Duplicate cultures were used for each dose. Preliminary growth inhibition test was conducted to determine the cytotoxicity of the chemicals. Chromosome specimens were stained with 3% Giemsa solution for 8 min. The number of cells with chromatid- and chromosome-type breaks and exchanges were scored per 200 cells at each dose. Polyploid cells were also scored per 800 cells at each dose.

Result : IPN tested negative for the induction of chromosomal aberration or anin CHO/IU cells.

Test substance : Isophthalonitrile
20.07.2005

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : other: Combined 28 day feeding study and one generation reproduction study
In vitro/in vivo : In vivo
Species : Rat
Sex : Male/female
Strain : Other: Charles River CD VAF/PLUS©
Route of admin. : Oral feed
Exposure period : -
Frequency of treatm. : -
Duration of test : Up to 122 days
Doses : 0, 5, 10, 25 and 50 mg/kg/day
Control group : yes
Method : -
Year : 2000
GLP : yes
Test substance : Isophthalonitrile

Method : Doses/concentration level: 0, 5, 10, 25 and 50 mg/kg/day. The concentration of test material administered to the rats was adjusted weekly in order to achieve as closely as possible the desired dietary intake of treatment. The achieved dosages of test material were calculated at the end of each week based on the dietary concentrations and body weights and food consumption for that week. After initiation of mating on Study Day 81, diets were prepared weekly at constant concentration based on Week 11 body weight and food consumption data for the remainder of the study. Age at study initiation: Rats were 29 days of age at receipt and 45 days of age at initiation of the test material administration. Control group

and treatment: Control animals were fed Purina© Certified Rodent Chow No. 5002 without test substance ad libitum and fresh tap water was available ad libitum. Study design: Initially, 25 rats of each sex were assigned to each group. Ten animals per sex from each group were killed after at least 31 days on the test diets, and the remaining 15 of each sex per group were exposed to isophthalonitrile for a total of at least 122 days. For the one-generation reproduction phase, mating commenced of Week 11. Rats were mated for a total of 14 days during which no body weight or food consumption measurements were recorded.

Result : NOAEL (NOEL): A NOEL was not established in male rats because of the increased incidence of hyaline droplet formation in the kidneys of males at all dietary levels: 5 mg/kg/day for females in the 28-day feeding phase and 25 mg/kg/day for the reproductive phase. The concentration of test material administered to the rats was adjusted weekly in order to achieve as closely as possible the desired dietary intake of treatment.

Compound-related effects on body weight and body weight gain with corresponding changes in food consumption were observed in males at 25 and 50 mg/kg/day and females at 10, 25 and 50 mg/kg/day during the 28-day feeding phase of the study. Clinical chemistry analyses revealed significant increases in ALT in males at 10 and 50 mg/kg/day and in females at 10 mg/kg/day and higher. In addition, serum cholesterol was higher in high-dose males than controls. Urine volume was higher and specific gravity was lower in males at 25 and 50 mg/kg/day and females at 50 mg/kg/day. Histopathologic examinations revealed compound-related increases in the incidence of centrilobular hepatocytomegaly in males and females at 50 mg/kg/day and males at 25 mg/kg/day. Furthermore, a compound related increase in hyaline droplet formation was noted in the kidneys of males when compared to controls. No females exhibited this finding. Hyaline droplet formation in the proximal tubular epithelium of kidneys in male rats is indicative of abnormal accumulation of alpha-2 m-globulin, a protein reported to be unique to the rat. Therefore, the No-Observed-Effect Level (NOEL) was considered separately for males and females. Based on the reductions in body weight, body weight gain, food consumption and increases in ALT at 10 mg/kg/day and higher, the NOEL for females in the 28-day feeding phase was 5 mg/kg/day. A NOEL was not established in male rats because of the increased incidence of hyaline droplet formation in the kidneys of males at all dietary levels. In the reproduction phase, parental reproductive parameters appeared to be unaffected by isophthalonitrile administration. Effects on parental body weight and body weight gain similar to those seen during the 28-day feeding phase were noted during the reproduction phase of the study at 25 and 50 mg/kg/day. Apparent compound-related reproductive effects on offspring survival in utero were noted. This was evidenced by an increase in the number of stillborn pups with a corresponding decrease in the number of live born pups and litter size at 50 mg/kg/day, suggesting that isophthalonitrile is fetotoxic at this dietary concentration. Similar effects were not observed at lower dietary concentrations, suggesting that 25 mg/kg/day is the NOEL for reproductive effects.

Test substance : ISOPHTHALONITRILE (CAS # 626-17-5) Test material provided by ISK Biotech Corporation. The test material was characterized for purity and identity prior to initiation and after completion of the study. Results indicated the test material was greater than 98% pure and was stable throughout the duration of the study.

Conclusion : A NOEL was not established in male rats because of the increased incidence of hyaline droplet formation in the kidneys of males at all dietary levels. No compound-related effects were seen on mating, fertility or gestation length.

Reliability : (2) valid with restrictions
2E: Meets generally accepted scientific standards, well documented and acceptable for assessment

20.07.2005 (1)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Epidemiology

Remark : No reports of adverse effects were reported in a 15-yr review of industrial experience of m-phthalodinitrile. It was reported that the probable reason for the lack of systemic effects of IPN is that, unlike aliphatic, nitriles do not liberate cyanide in the body.

Reliability : (4) not assignable
4C/4D Original reference not yet available. Original reference in foreign language

20.07.2005 (21)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT